CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75611

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-611** Date of Submission: **March 29, 1999**

Applicant's Name: **Torpharm**

Established Name: **Famotidine Tablets USP, 20 mg & 40 mg**

Labeling Deficiencies

1. CONTAINER: (20 mg and 40 mg – 30's, 100's, and 1,000's)

   Revise the storage temperature statement to read "Store at Controlled Room Temperature 15^0 - 30^0C (59^0 – 86^0F)[see USP].

2. INSERT

   a. GENERAL

   Due to numerous and significant differences between your proposed labeling and labeling of the reference listed drug, Pepcid (Merck Research Laboratories), approved March 18, 1999, revise your labeling to be in accord with the attached copy of that labeling.

   b. DESCRIPTION

      i. Revise the second sentence of the first paragraph to read "Famotidine is [1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl]thio]propylidene]sulfamide.

      ii. Replace "empirical" with "molecular" in the third sentence of the first paragraph.

      iii. May delete , from the list of inactive ingredients.

   c. CLINICAL PHARMACOLOGY

   Pharmacokinetics

   Add as the second sentence in the first paragraph "Famotidine tablets and famotidine oral suspension are bioequivalent." Reference to the orally disintegrating tablets should not be included since it is still protected by patents.

   d. ADVERSE REACTIONS

   Add following as the last paragraph.

   "The adverse reactions reported for famotidine tablets may also occur with famotidine oral suspension."

   e. DOSAGE AND ADMINISTRATION

   Please add a new subsection entitled "Oral Suspension" with the following sentence just before the "Concomitant Use of Antacids" subsection.

   "Famotidine oral suspension may be substituted for famotidine tablets in any of the above indications."

   f. HOW SUPPLIED

   See CONTAINER comment.

Please revise your labels and labeling as instructed above and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labels and labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the last submitted labeling with all differences annotated and explained.

_____

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ATTACHMENT

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation – see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. [see FTR]		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T □ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

FOR THE RECORD:

1. MODEL LABELING

RLD Info: RLD labeling is Pepcid®; Merck; issued November 1998, Approved March 18, 1999 (NDA 19-462/S-027).

2. INACTIVE INGREDIENTS

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients of components and composition statements on page 1220, vol. 1.3.

3. PATENTS/EXCLUSIVITIES

Patent # 4,283,408 EXPIRES October 15, 2000, and there is no protected marketing exclusivity. Firm cites Paragraph IV Certification.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Preserve in well-closed containers, protected from light.
NDA: Avoid storage at temperatures above 40^0C (104^0F)
ANDA: Store at 25^0C (77^0F); excursions permitted to 15^0 - 30^0C (59^0 – 86^0 F)[see USP Controlled Room Temperature].

Firm will be informed to revise to "Store at Controlled Room Temperature 15^0 - 30^0C (59^0 – 86^0 F)[see USP].

5. DISPENSING STATEMENT COMPARISON

USP: Preserve in well-closed containers, protected from light.
NDA: No recommendation.
ANDA: Protect from light. Dispense in a tight, light resistant container.

6. PACKAGING CONFIGURATIONS

RLD: 20 mg and 40 mg - Unit-of-use bottles of 30's with CRC, Unit-of-use bottles of 100's with CRC, bottles of 1,000's & 10,000's and unit dose cartons of 100's

ANDA: 20 mg and 40 mg - Bottles of 30's, 100's and 1000's

7. CONTAINER/CLOSURE SYSTEM

Container - HDPE
CLOSURE - 30's – CRC
100's & 1000's – Non–CRC

See pages 1934 Vol. 1.5

8. The descriptions of the tablets in the HOW SUPPLIED section are consistent with that of the application. See pages 2087 and 2090 in vol.1.6.

9. SCORING

NDA - Not specified
ANDA - Unscored

10. CLINICAL PHARMACOLOGY (Pharmacokinetics)

The third sentence comparing tablets and oral solution dosage forms has been omitted. It was decided within DLPS that the reference to famotidine oral suspension should be included since it was off patent and to omit the orally disintegrating tablets since it is still protected by patents.

Date of Review: October 7, 1999

Date of Submission: March 29, 1999

Primary Reviewer: Koung Lee /S/

Date: 10/7/99

Team Leader: Charlie Hoppes /S/

Date: 10/7/99

cc:

ANDA: 75-611
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSNZ\TORPHARM\LTRS&REV\75611NA1.Labeling Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-611** Date of Submission: **November 8, 1999**

Applicant's Name: **Torpharm** Established Name: **Famotidine Tablets USP, 20 mg & 40 mg**

Labeling Deficiencies

INSERT

a. GENERAL

Delete all trailing zeroes after the decimal point.

b. DESCRIPTION

Revise the molecular weight to 337.45.

c. CLINICAL PHARMACOLOGY IN ADULTS

Pharmacokinetics

Revise the second sentence in the first paragraph to read as, "Famotidine tablets, famotidine oral suspension, and famotidine orally disintegrating tablets are bioequivalent." and switch the sentence around with the third sentence.

d. CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS

Add "1.3 ± 0.2" under "Volume of Distribution (V_d)(L/kg) for adults in Table 6.

e. ADVERSE REACTIONS

Revise the last paragraph to read as, "The adverse reactions reported for famotidine tablets may also occur with famotidine oral suspension and famotidine orally disintegrating tablets."

f. DOSAGE AND ADMINISTRATION

Please add a new subsection entitled "Orally Disintegrating Tablets" with the following sentence just before the "Concomitant Use of Antacids" subsection.

"Famotidine orally disintegrating tablets may be substituted for famotidine tablets in any of the above indications at the same recommended dosages."

Please revise your labeling as instructed above and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labels and labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research